

## Circadian Rhythms and Sleep

# Delayed Phase Jumps of Sleep Onset in a Patient With Non-24-Hour Sleep-Wake Syndrome

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**Summary:** We studied a 30-year-old man with non-24-hour sleep-wake syndrome. To investigate the relationship between environmental light-dark cycles and his sleep-wake rhythm, we documented his sleep log and rectal temperature data without any therapeutic interventions. We found that 1) the patient's sleep-wake pattern consisted of two different components, appearing alternatively, with a period of 27.2 days: regular free-run (R free-run), consisting of a daily 30- to 60-minute regular delay of sleep onset; and jumping free-run (J free-run), with clusters of delayed (>4 hours) phase jumps in sleep onset (DP jump); 2) the frequency of sleep onset was higher during late evening hours to midnight hours than in the daytime; 3) DP jumps occurred exclusively when the prior sleep onset was delayed into the daytime; and 4) a cluster of DP jumps was likely to start when the patient's low temperature zone (a period in which rectal temperature was below average) at subjective night was illuminated by sunlight. These results suggest that DP jumps in the patient may occur due to illumination of the delay portion of the phase-response curve. **Key Words:** Non-24-hour sleep-wake syndrome—Circadian rhythm—Core body temperature—Phase-response curve—Bright light pulse.

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The environmental light-dark cycle is a major regulator of the human circadian rhythm (1). Experimental elimination of these environmental time cues in human subjects results in a sleep-wake cycle that is longer than 24 hours (free-run) (2-5). Miles et al. (6) first reported the non-24-hour sleep-wake syndrome (non-24 syndrome) (7) in a blind subject who displayed a free-running sleep-wake cycle. Several authors described similar conditions in blind subjects (8-10). Subsequent reports documented non-24 syndrome in sighted subjects living in normal environments (11-16). Many authors have suspected that the pathogenesis of non-24 syndrome may be related to a disturbance in the entraining mechanism of the circadian clocks of subjects with the syndrome. However, no clear documentation has been made with respect to these hypotheses. Here we report on a sighted male patient with non-24 syndrome and we document the

relationship between environmental light-dark cycles and his sleep-wake rhythm.

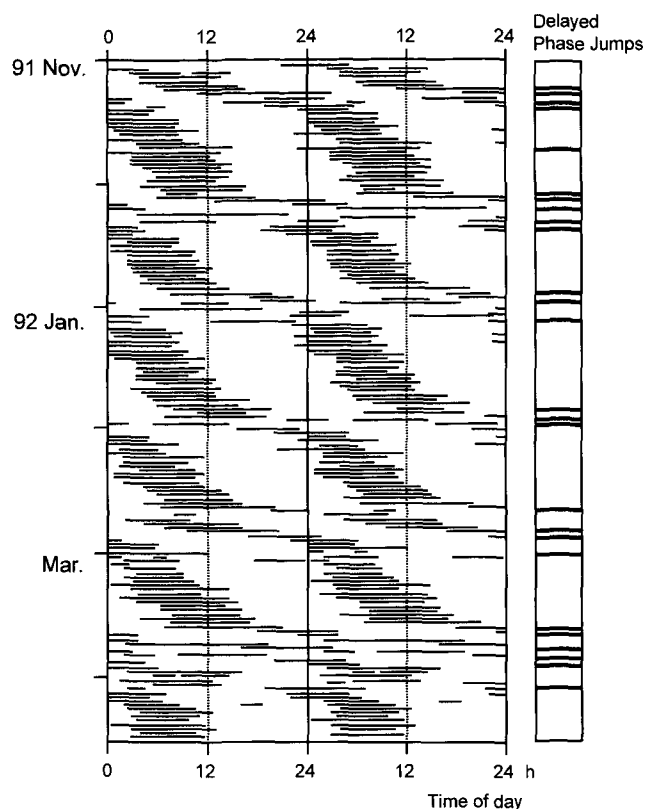
### Case report

We report on a 30-year-old man, who, at the age of 18, began to notice that his sleep onset was gradually delayed by approximately 1 hour each day. He tried to maintain regular retiring and waking times but was unable to succeed because of marked difficulties in falling asleep. This tendency continued for 4 years, when he was studying industrial design in college. When he graduated, he started working as a designer at a studio with a flexible time schedule. Walking to work about an hour after his natural wake time, he worked for 8 hours and then returned home. No abnormal findings were detected in routine electroencephalograms (EEG), brain magnetic resonance imaging (MRI) investigations, blood count, biochemistry, or thyroid functions. A semi-structured psychiatric interview revealed that he had no axis I or III disorders (17).

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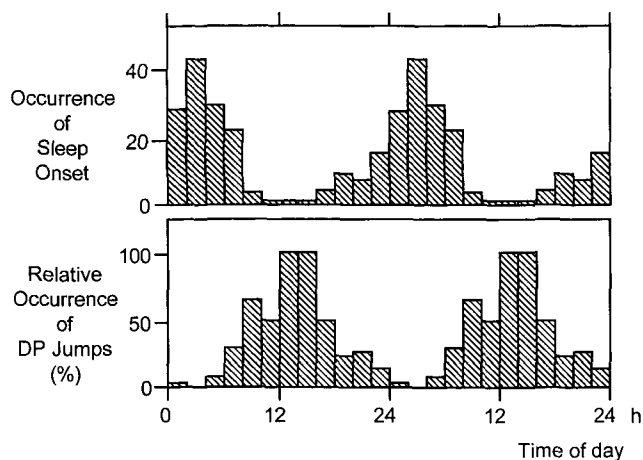


**FIG. 1.** The patient's sleep-wake record during the drug-free observation period is double-plotted in raster format. The sleep-wake rhythm of the patient was found to consist of two different components, each of which alternated, with a period of  $27.2 \pm 0.6$  days (mean  $\pm$  SE): a free-running sleep-wake cycle, with a daily 30- to 60-minute delay of sleep onset, as typically seen from November 12 through December 4, 1991 or from December 12 through December 28, 1991 (regular free-run; R free-run); and a less regular cycle, with clusters of DP jumps, as seen from December 5 through December 11 or December 29, 1991 through January 4, 1992 (jumping free-run; J free-run). Switch from R-free-run to J free-run seemed to occur where the patient's sleep onset was delayed into the morning or afternoon hours.

## METHODS

We asked the patient to keep a detailed sleep log, including the times of lights off and on, times of sleep onset and awakening, and his major daytime activities. Verification of sleep log data on later occasions with an ambulatory activity monitoring machine revealed that his sleep log data were accurate, but we did not verify them on this occasion. A delay of sleep onset longer than 4 hours was defined as a delayed-phase jump (DP jump). We expressed the temporal frequency distribution of sleep onset preceding a DP jump as a percentage of the total number of sleep onset events per 2-hour period (the relative occurrence of DP jumps).

Rectal temperature measurements were made at 5-minute intervals from March 4 through April 8, 1992 using an ambulatory recorder (resolution  $0.01^\circ\text{C}$ ;



**FIG. 2.** Temporal distributions of sleep onset and relative occurrence of DP jumps for the 164 days (same as Fig. 1) were documented. The occurrence of sleep onset per 2-hour period was higher at night than during the day (upper histogram). A delay of sleep onset longer than 4 hours was defined as a DP jump. We expressed the temporal frequency distribution of sleep onset preceding DP jump as a percentage of the total number of sleep onset events (the relative occurrence of DP jumps). The relative occurrence of DP jumps reached 100% when sleep onset occurred in the daytime (0800–1600 hours), whereas it was lower during nighttime (lower histogram).

Kohden Medical Inc., Tokyo, Japan) (18). We defined a period when the rectal temperature was below the overall mean of the measuring period ( $36.93^\circ\text{C}$ ) as a low-temperature zone (LT zone).

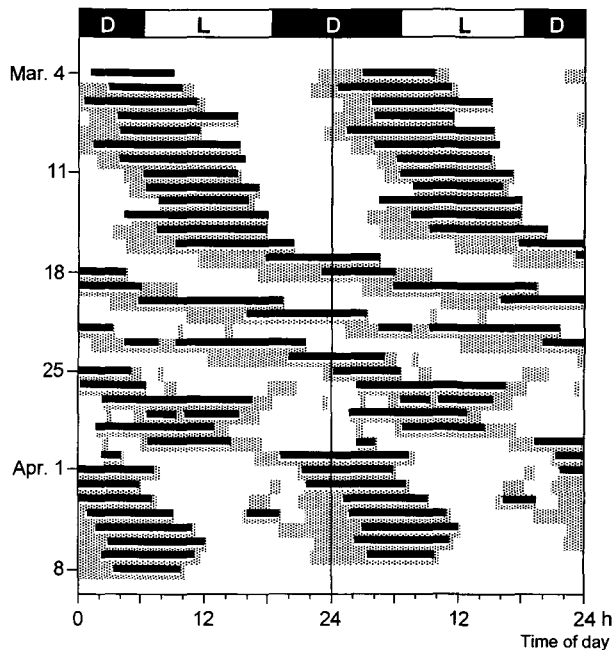
## RESULTS

### Overview

The patient's natural sleep-wake rhythm without therapeutic intervention (164 days) is documented in Fig. 1. The sleep-wake rhythm of the patient was found to consist of two different components, each of which alternated, with a period of  $27.2 \pm 0.6$  days [mean  $\pm$  standard error (SE)]; a free-running sleep-wake cycle, with a daily 30- to 60-minute delay of sleep onset (regular free-run; R free-run); and a less regular cycle, with clusters of DP jumps (jumping free-run; J free-run). His sleep-wake cycle showed R free-run when he fell asleep during evening or midnight hours. Once his sleep onset was delayed into the morning hours, his sleep-wake cycle resulted in J free-run.

### Circadian features of sleep onset and DP jump

Figure 2 represents temporal distributions of sleep onset and the relative occurrence of DP jumps for the 164 days. The sleep onsets occurred more frequently from the late evening to midnight compared to the



**FIG. 3.** Rectal temperatures and sleep-wake patterns were monitored during the drug-free observation period. Sleep (black horizontal bars) and low temperature (LT) zone (gray horizontal bar, see text) are double-plotted in raster format. From March 4 through 16, 1992 (R free-run) the sleep and the LT zones were delayed each day, regularly, in a period of 24.6 hours. The sleep episodes started  $2.1 \pm 0.4$  (mean  $\pm$  SE) hours subsequent to the onsets of the LT zone and terminated approximately at the end of the LT zone. From March 17 through March 25, 1992 (J free-run) the sleep episodes display DP jumps, whereas LT zones appear almost regularly, with a 31.2-hour cycle. The sleep onsets were further delayed relative to the onset of LT zones ( $7.1 \pm 1.5$  hours). On April 1, 1992 the patient started R free-run with a 24.6-hour cycle.

daytime hours (Fig. 2, top). The frequency of sleep onset was the highest during 0200–0400 hours and lowest during 1000–1600 hours. The relative occurrence of DP jumps was higher in the daytime (0800–1600 hours), whereas it was apparently lower during the night (Fig. 2, bottom).

### Relation between sleep and core body temperature

Sleep episodes and LT zones are summarized in Fig. 3. When the patient displayed R free-run between March 4 and 16, 1992 his sleep episodes and LT zones appeared regularly, in a period of 24.6 hours. The sleep episodes started  $2.1 \pm 0.4$  (mean  $\pm$  SE) hours subsequent to the onsets of LT zones and terminated approximately at the end of LT zones. When the patient displayed J free-run (from March 17 to 25, 1992), LT zones appeared almost regularly, with a 31.2-hour cycle. The sleep onsets were further delayed relative to the onset of LT zones ( $7.1 \pm 1.5$  hours). On April 1, 1992 the patient started R free-run with a 24.6-hour cycle.

### DISCUSSION

In this study, the patient's sleep-wake pattern was found to consist of two different components that alternated, with a period of 27.2 days: R free-run, consisting of a 30- to 60-minute regular delay of sleep onset each day; and J free-run, with clusters of DP jumps. In this respect, most of the prior reports (11–16) on sighted non-24 syndrome seemed to have a similar mixture of two different free-run patterns. We also found that the cluster of DP jumps started when the prior sleep onset was delayed into morning hours. This may indicate that the light-dark cycle modulated the patient's sleep-wake cycle, especially the switch from R free-run to J free-run. Analyses of the circadian features of sleep onset and DP jump revealed that the frequency of sleep onset was higher during late evening and midnight hours than the daytime. Wollmann and Lavie (14) found similar circadian features of sleep onset in a patient with non-24 syndrome. They speculated that such circadian features of sleep onset may be explained by the "forbidden zone" for sleep onset in the daytime and the early evening (14). In the course that our patient exhibited, however, sleep onset might fail to stay in the daytime because of the frequent occurrence of DP jumps.

The further prolongation of the sleep-wake cycle in J free-run recalls the internal desynchronization between sleep-wake cycle and rectal temperature in a long isolation experiment (2). In the present case, however, phase jumps of both sleep and LT zone in J free-run seemed to occur almost in parallel. The intervals between onsets of LT zone and sleep were different between R free-run (2.1 hours) and J free-run (7.1 hours). This indicates that in J free-run, sleep was more delayed relative to rectal temperature. Kokkoris et al. (11) reported on a patient with non-24 syndrome and found that a sleep-wake cycle longer than 24.8 hours was accompanied by the appearance of a rectal temperature trough that occurred earlier relative to sleep onset. Their observation may also indicate that the sleep-wake cycle was more delayed relative to the core body temperature rhythm when the patient exhibited the longer sleep-wake cycle (11).

Hoban et al. (15) evaluated the serum melatonin rhythm in dim light conditions in a patient with non-24 syndrome and suggested that the sleep-wake cycle was more delayed relative to the melatonin rhythm. They postulated that this delayed bedtime, accompanied by a later awakening, might cause the patient to sleep through the phase advance portion of her phase-response curve (PRC) to light (15). More recently, we reported that the interval between rectal temperature nadir and sleep offset was prolonged in patients with delayed sleep phase syndrome (DSPS) compared to

control subjects (19). This indicates that prolonged morning sleep resulted in failure to utilize the advance portion of the PRC. Such an estimated inability to phase-advance the circadian rhythm properly may be common in sleep disorders featuring sleep phase delay, as Weitzman et al. (20) originally supposed.

Hoban et al. (15) postulated that the delayed bedtime may have caused the patient's delay portion of the PRC to be illuminated if the patient went to bed during the daytime. Recent findings (5) on the human PRC to light indicated that light exposure slightly after the temperature nadir possibly induced a phase advance of the circadian rhythm, and that light exposure slightly before the temperature nadir induced a phase delay. Given that the LT zone corresponds to a high melatonin period (i.e. circadian night), their hypotheses (5) may be applied for our patient. The present patient may have had an opportunity to be illuminated on his delay portion by the sun when he walked back home in the morning. We speculate that this illumination of the delay portion of the PRC may be responsible for the provocation of DP jumps, resulting in the alternating appearance of two different periods of the sleep-wake cycle.

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## REFERENCES

1. Moore-Ede MC, Czeisler CA, Richardson GS. Circadian time-keeping in health and disease. I. Basic properties of circadian pacemakers. *N Engl J Med* 1983;309:469-76.
2. Wever RA. The circadian system of man. In: *Topics in environmental physiology and medicine*. New York: Springer-Verlag, 1979.
3. Czeisler CA, Allen JS, Strogatz SH, et al. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. *Science* 1986;233:667-71.
4. Honma K, Honma S. A human phase response curve for bright light pulse. *Japan J Psychiatry Neurol* 1988;42:167-8.
5. Minors DS, Waterhouse JM, Wirz-Justice A. A human phase-response curve to light. *Neurosci Lett* 1991;133:36-40.
6. Miles LE, Raynal DM, Wilson MA. Blind man living in normal society has circadian rhythms of 24.9 hours. *Science* 1977;198:421-3.
7. Diagnostic Classification Steering Committee, Thorpy MJ, chairman. *International classification of sleep disorders: diagnostic and coding manual*. Rochester, MN: American Sleep Disorders Association, 1990.
8. Arendt J, Aldhouse M, Wright J. Synchronization of a disturbed sleep-wake cycle in a blind man by melatonin treatment. *Lancet* 1988;1:772-3.
9. Okawa M, Nanami T, Wada S, et al. Four congenitally blind children with circadian sleep-wake rhythm disorder. *Sleep* 1987;10:101-10.
10. Folkard S, Arendt J, Aldhouse M, Kennett H. Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. *Neurosci Lett* 1990;113:193-8.
11. Kokkoris CP, Weitzman ED, Pollak CP, Spielman AJ, Czeisler CA, Bradlow H. Long-term ambulatory temperature monitoring in a subject with a hypernycthemeral sleep-wake cycle disturbance. *Sleep* 1978;1:177-90.
12. Weber AL, Cary MS, Connor N, Keyes P. Human non-24-hour sleep-wake cycles in an everyday environment. *Sleep* 1980;2:347-54.
13. Kamgar-Parsi B, Wehr TA, Gillin C. Successful treatment of human non-24-hour sleep-wake syndrome. *Sleep* 1983;6:257-64.
14. Wollman M, Lavie P. Hypernycthemeral sleep-wake cycle: some hidden regularities. *Sleep* 1986;9:324-34.
15. Hoban TM, Sack RL, Lewy AJ, Miller LS, Singer CM. Entrainment of a free-running human with bright light? *Chronobiol Int* 1989;6:347-53.
16. Okawa M, Uchiyama M, Shirakawa S, Takahashi K, Mishima K, Hishikawa Y. Favorable effects of combined treatment with vitamin B12 and bright light for sleep-wake disorders. In: *Sleep-wakefulness*. New Delhi: Wiley Eastern Ltd., 1993.
17. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 3rd edition-revised. Washington DC: American Psychiatric Association, 1987.
18. Uchiyama M, Mayer G, Okawa M, Meier-Ewert K. Effects of vitamin B12 on human circadian body temperature rhythm. *Neurosci Lett* 1995;192:1-4.
19. Ozaki S, Uchiyama M, Shirakawa S, Okawa M. Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. *Sleep* 1996;19:36-40.
20. Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement WC. Delayed sleep phase syndrome: a chronobiological disorder with sleep-onset insomnia. *Arch Gen Psychiatry* 1981;38:737-46.